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M16-04 **Lung Cancer in Women, Tue, Sept 4, 10:30 - 12:00**

Women's smoking in the 21st century: trends, determinants and cessation

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I. Smoking and Tobacco Use Prevalence in Developed and Developing Nations

Tobacco use among women is undergoing dynamic and rapid shifts throughout the world. It is estimated that 250 million women (11% of women worldwide), compared to almost 1 billion men, in the world are daily smokers: 22% in developed nations vs. 9% in developing nations (compared to 35% of men vs. 50% of men, respectively). Oral tobacco use is far more prevalent in South Asia, and may be as high as 30% in women, compared to 25% in men. In many developed nations, notably the USA, Canada, the UK and Australia, smoking among women continues to slowly decline, but in several European countries (southern, central and eastern) there has not been a decline and smoking may even be increasing. From 1960-2004, smoking prevalence has remained relatively stable in Japan (15%-17%); in the UK, it decreased from 42% to 24%; and in the USA it decreased from 34% to 19%. The top ten countries with the highest reported smoking rates among women (2005 or latest available data) are: Cook Islands (71%), Nauru (59%), Guinea (47%), Chile (37%), Serbia & Montenegro (34%), Kiribati, FYR Macedonia (32%), Lebanon, Tuvalu (31%), and Boznia & Herzegovina (30%). The comparison top 10 countries for men are: Yemen (77%), Djibouti (75%), Cambodia, China (67%), Kazakhstan, Rep. Korea (65%), Armenia (62%), Albania, Russian Federation, Samoa (60%), and Guinea (59%).1

Unfortunately, tobacco use among girls is rising worldwide; there were no gender differences in smoking among half of the countries surveyed in the Global Youth Tobacco Survey, and girls have higher smoking rates than boys in some parts of Europe (e.g., Austria, Czech Republic, Portugal, Spain, Sweden, Norway) and South America (e.g., Argentina). Factors increasing girls smoking are similar in both sexes: industry marketing, easy access, affordability, peer smoking and influence, parental modeling and normative behavior. Both girls and boys still believe that smoking enhances one's image and increases popularity; and girls smoke to control weight. In many countries, smoking still appears in movies, magazines, on billboards and other media targeted to youth conveying positive social, physical and style images. Broader buying power, women's emancipation and relaxation of cultural strictures are other factors associated with greater female smoking.1

II. Major Biobehavioral Variables in Women's Smoking & Tobacco Use: Biological Determinants and Social Factors

Among the biological variables determining women's smoking behavior, nicotine dependence has been most thoroughly explored. Perkins2 has been the major proponent of the view that women find nicotine less reinforcing than men and are more responsive to smoking cues, but this hypothesis has not been supported by pharmacologic trials that show women to be equally responsive to NRT and bupropion (see below). There may be gender-specific genetic variation in nicotine dependence among subgroups of women,3 which might account for women with greater nicotine dependence having less success in cessation. Depression and negative affect in general have been considered of greater importance in controlling women's smoking behavior as well as a number of other factors including weight maintenance or loss, and the role of hormonal and menstrual factors.4 Pregnancy is considered a "teachable moment" for smoking cessation, when many women quit spontaneously. However relapse is still very high after childbirth, and successful interventions to promote abstinence during childrearing are still much needed. Among the social and societal factors affecting smoking, peer influence and norms, parental behavior and approval, perceived risks, attitudes and beliefs about smoking, the influence of media, marketing and policy initiatives remain very important, even more in the developing than in the developed nations.

III. Smoking Cessation

Studies on smoking cessation have largely been conducted in the developed world. There is a dearth of information on needs assessment and cessation in the developing nations.

A. Population-based vs. clinical data: do women have lower quit rates than men?

There is no consistent agreement on whether women have greater difficulty stopping smoking than men. In the USA, population data do not demonstrate meaningful gender differences in the percentage of women and men current smokers who want to quit (72.2% F vs 68.0%M), and who quit for more than one day (41.9%F vs. 40.2%M).5 It has been hypothesized that population surveys favoring males over females in cessation rates could be accounted for by men switching from cigarettes to other forms of tobacco, such as cigars or snus. Analysis of California population prevalence data regarding smoking cessation

with and without assistance, in 1996, showed that women were more likely to use all methods of assistance (counseling, nicotine replacement [NRT], counseling + NRT) than men (22.1% vs. 18.3%) and that usage increased with age. Use of assistance was also associated with higher long term (12 month) quit rate across gender (15.2% vs. 7.0%).6

In formal cessation programs some studies do show men having higher quit rates than women. For example, Wetter et al7 examined 3 RCTs of nicotine patch treatment (N=632). Men had higher abstinence rates than women at all follow-ups. Multiple mediators were examined but none accounted for the gender difference (demographics, smoking history, pre-cessation affect/depression, smoking outcome expectations, coping style, health symptoms, post-cessation withdrawal/affect/stress). Killen et al8 analyzed the data from 4 trials encompassing 13 studies, with a total of 2086 participants. Quit rates were not significantly different for men and women. Gender was not a moderator within subgroups matched for established moderators, such as nicotine dependence. These authors state that their analyses generalize to formal intervention programs, including physician advice, with less intensive behavioral components (short of individual or group counseling), but perhaps not to studies of (population-based) spontaneous cessation. Interestingly, Swan et al9 identified wide heterogeneity among men and women in a large randomized controlled trial (RCT) of bupropion and counseling, which involved 875 F and 649M). Heterogeneity was greater in women, but women also had a subgroup with the highest rate of quitting (42% at 12 months). This group was characterized by higher education, longer quit attempts, low levels of stress, higher adherence to medication, and the lowest dropout from medication. The group of women with the lowest quit rate (9.8% at 12 months) was characterized by high BMI, low prior quit rates, low adherence to medication and greater likelihood of discontinuing medication. Overall, the rate of nonsmoking among women (27.5%) was lower than among men (32.8%, p. <0.04). There was no treatment X individual characteristics interaction. The authors recommend tailoring interventions to subgroups at highest risk of relapse. In another study,10 a RCT of a group program followed by basic support vs. enhanced (tailored and targeted) telephone counseling, there was a significant treatment X gender interaction. In the enhanced group, men had higher quit rates through 15 month follow-up and lower relapse; women fared better in the basic support condition and did more poorly in rate of relapse. However, women did not have a lower success rate overall or a higher relapse rate; in fact, there was a trend for superior quitting. History of depression did not interact with condition. Several studies below, using pharmacotherapy, found gender differences favoring men, in smoking cessation. although not interacting with drug treatment. Thus, these studies produce a variety of suggestive findings and stimulus for further research but no clear outcome on gender differences in success in quitting and remaining abstinent.

B. Do men and women respond differently to pharmacologic treatment (i.e., do women do more poorly)?

Several recent studies have clarified that there are no gender differences in response to the major pharmacologic treatments for smoking cessation, nicotine replacement and bupropion. Shiffman et al11 conducted a secondary analysis of 2 RCTs, which used 21 mg nicotine patch and 2- and 4-mg nicotine lozenge; outcomes were 6 month continuous abstinence and survival analysis. Active NRT was more effective than placebo among women for both patch and lozenge. In the lozenge trial, women were less successful than men, overall. The gender X treatment interaction was not significant in either study, so there was no evidence of differential treatment efficacy by gender. In the lozenge trial, gender moderated the effects of smoking rate and dependence (but not treatment) on outcome; thus, more dependent women smokers had lower quit rates. Dependence predicted failure among women, but not men. In another study, Scharf and Shiffman12 examined gender differences in smoking cessation with and without bupropion, using pooled- and metanalyses of clinical trials of bupropion (4421 participants in 12 RCTs). Bupropion was an effective smoking cessation aid for women and there was no treatment X gender interaction; women and men benefitted equally. However, women were less successful at quitting, overall. Thus, pharmacotherapy appears to be equally effective for women and men, but lingering questions remain about the overall success rates of cessation.

IV. Future Research Needs

There is much to be learned about the biobehavioral basis of smoking and cessation, particularly in the areas of genetic determinants, nicotine dependence, affect, and the role of hormonal or other physiological factors. Basic behavioral aspects of smoking in women are also in need of further exploration, especially the role of sensory cues, and interpersonal factors such as the need and type of support during cessation. Thus, the benefits of tailoring for cessation treatment and relapse prevention have been hypothesized but not yet established. The literature suggests the existence of complex interactions among gender, biological and social variables, and cessation treatment.11 Cessation interventions at "teachable moments" in the (female) life cycle merit more research, such as pregnancy and child-rearing. These also include the impact of major illness (CVD, cancer, diabetes) in women, or childhood illnesses such as respiratory infections and asthma that promote parental cessation to reduce second hand smoke exposure. A major area for further research is women's tobacco use in the developing world: why do women begin to smoke and how to best help them stop; protecting nonsmoking norms while balancing social emancipation and financial independence; and the influence of policy and economic issues. Many of these future research needs were set down in a major conference document.13 This is an exciting area and complex topic, and one deserving of a substantial effort in research and public education.

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Session M17: Novel Vaccines and Immunotherapy

M17-01 **Novel Vaccines and Immunotherapy, Thur, Sept 6, 10:30 - 12:00**

Immunotherapy for lung tumors

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Introduction: Non small cell lung carcinoma (NSCLC) is a non-immunogenic cancer. Unlike in melanomas, tumor infiltrating lymphocytes of the effector cell phenotype are not present in the tumor. NSCLC tumor cells thus have never been exposed to effector cells and, unlike melanoma, have not been selected to resist cytotoxic T lymphocyte (CTL) attack. Would NSCLC tumors be able to resist CTL, if CTL are generated by vaccination?

We designed two types allogeneic, whole cell NSCLC vaccines, generated from an NSCLC cell line (AD100) established in Miami and conditioned to continuous growth in standard cell culture media. Genomic analysis of the morphological types of NSCLC, including squameous carcinoma, show largely overlapping genetic up- and downregulation of several hundred genes in the different cell types (1).

The B7- vaccine: The AD100 cell line was cotransfected with CD80 (B7.1) and HLA A1 to render the cells immunogenic. Cells are irradiated to prevent replication, but remain alive for several days when placed in culture. The in vivo immunogenicity of the vaccine is based on B7.1 expression which stimulates NK cell activation.

Allogenicity and HLA A1 expression prevents engagement of killer inhibitory receptors (KIR) and inhibition of NK mediated cytotoxity. NK activation and killing of vaccine cells produces IFN- γ and releases tumor antigens. Dendritic cells and macrophages are attracted and take up released tumor antigens and cross present them to CD8 T cells differentiating into CTL.

In a phase I study 19 patients were enrolled with stage IIIB/IV NSCLC who had failed several lines of prior therapy. They were treated by intracutaneous injection of 5x107 AD100-HLAA-B7.1 cells every two weeks for a maximum of nine vaccinations. The vaccine was safe causing no vaccine related serious adverse event. The immune response was measured by analyzing purified CD8 cells stimulated in vitro with vaccine cells for IFN-γ production by Elispot assays. All but one patient had a significant immune responses. The mean response after three vaccinations was the generation of 160 NSCLC specific CD8 CTL per ml of blood from a pre-immunization level of 0-1 CTL/ml. After 6 and 9 vaccinations the NSCLC specific CTL level increased to 220 CTL/ml. One year survival was 47%, two year survival 32%. Six patients had a clinical response, rated as stable disease in 5 patients and a minor response in one.

Although uncontrolled the study showed a definite trend towards clinical benefit of B7 vaccination. We are currently conducting two phase II studies to determine effectiveness and to study the clinical response in patients with undetectable disease after surgery and chemotherapy.

The gp96-vaccine: Gp96 is the one of the major protein and peptide chaperones of the endoplasmatic reticulum. It transports peptides on their way to MHC class I presentation and helps folding of membrane associated and secreted proteins during synthesis. Srivastava was the first (2)to show that gp96 isolated from tumor cells and injected into syngeneic mice was able to induce a tumor specific immune response that was able to protect mice from a subsequent challenge with the same tumor but not against other tumors. Gp96 is taken up by dendritic cells and macrophages via its endocytic receptor CD91 and causes activation of DC, independent of CD4 help and CD40-L/CD40 interaction. Uptake of gp96 and its chaperoned peptides results in cross presentation of the peptides by MHC I of the DC and priming of antigen specific cognate CD8 T cells.

To render gp96 suitable for a vaccine system with allogeneic cells, we genetically modified the protein by deleting its endoplasmatic reticulum retention signal and replacing it with the Fc portion of IgG1 (3). Gp96-Ig transfected tumor cells secrete gp96-Ig along with its chaperoned peptides. Injection of gp96-Ig transfected tumor cells into syngeneic mice results in tumor rejection associated with the clonal expansion of cognate CD8-CTL to a frequency of 15-40 of all CD8 cells (4). Clonal CD8 CTL expansion is enhanced in CD4 deficient mice while CD40-L